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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/733,893	12/11/2003	Michael S. German	02307O-138122US	2608

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EXAMINER	
POPA, ILEANA	
ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/733,893	GERMAN ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/04/2007 has been entered.

2. Claims 1-30 have been cancelled.

Claims 31-34 are pending and under examination.

Double Patenting

3. Claims 31, 33, and 34 remain rejected under the obviousness-type double patenting as claiming the same invention as claims 1, 3, 5, and 9 of the U.S. Patent No. 5,885,971, since Applicants did not submit a terminal disclaimer.

4. Claims 31-34 remain rejected under the obviousness-type double patenting as claiming the same invention as claim 6 of the U.S. Patent No. 6,004,944, since Applicants did not submit a terminal disclaimer.

5. Claims 31, 33, and 34 remain rejected under the obviousness-type double patenting as claiming the same invention as claims 1, 2, 4, 7, and 8 of the U.S. Patent No. 6,255,289, since Applicants did not submit a terminal disclaimer.

6. Claims 31-34 remain rejected under the obviousness-type double patenting as claiming the same invention as claim 1 of the U.S. Patent No. 6,531,455, since Applicants did not submit a terminal disclaimer.

7. Claims 31-34 remain rejected under the obviousness-type double patenting as claiming the same invention as claims 1, 3, and 5 of the U.S. Patent No. 6,566,342, since Applicants did not submit a terminal disclaimer.

Applicant agreed to submit a terminal disclaimer upon indication of allowable subject matter. The Applicants' comments are acknowledged, however the rejection will be maintained until a terminal disclaimer is filed or claims are amended to obviate the rejection.

Claim Rejections - 35 USC § 103

8. Claims 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hickman et al. (Human Gene Therapy, 1994, 5: 1477-1483), in view of both Yang et al. (Proc Natl Acad Sci USA, 1993, 90: 4601-4605) and Losordo et al. (Circulation, 1994, 89: 785-792).

Applicant argues that the Examiner did not establish a case of obviousness of the present claims over Hickman et al. and Yang et al. and also submits a declaration under 37 C.F.R. § 1.132, which addresses the Examiner's remarks in the final Office action of 02/12/2007 and shows that Hickman et al. and Yang et al. do not teach that intraductal administration of naked DNA is an efficient way to deliver proteins to the bloodstream, and that one of skill in the art would not have been motivated to modify the teachings of Hickman et al. in the manner proposed by the Examiner. Applicant argues that the suggestion to combine must be found in the prior art and not in Applicant's disclosure, i.e., the Examiner cannot use hindsight, that the prior art must be considered in its entirety, including portions that teach away from the claimed invention, and that the motivation to combine must be clear and particular. In his remarks and declaration, Applicant submits that there is no clear motivation in either Hickman et al. or Yang et al. to modify the method of Hickman et al. by using intraductal delivery of naked DNA. Applicant argues that, since Yang et al. teach a method for selective targeting of biliary epithelial cells over hepatocytes, one of skill in the art would not have been motivated to modify the method of Hickman et al., which, in contrast to the method of Yang et al., is focused on targeting hepatocytes. Applicant submits that Yang et al. teach the biliary epithelial cells as the primary target for the treatment of CF via gene transfer, and specifically teach away from the strategies that focus "exclusively on the hepatocyte as the target cell" (p. 4602, column 2, first full paragraph, p. 4604). Applicant argues that the Examiner's statement regarding Yang et al. teaching of some transfected hepatocytes via intraductal delivery does not reflect the totality of their teachings with

respect to transfection of hepatocytes. Applicant argues that Yang et al. teach that transfection of hepatocytes via the intraductal route is very inefficient, even with the adenovirus, a vector normally regarded as providing efficient gene transfer. Specifically, Applicant submits that Yang et al. teach that only the maximal dose of virus achieved significant gene expression in hepatocytes, while the next highest dose resulted in less that 1% of all heaptocytes being transfected (p. 4603, column 1, first full paragraph). Applicant asserts that this rapid diminishment of gene transfer to hepatocytes with the delivery of submaximal doses of adenoviral vector does not reasonably support a conclusion of efficient gene expression into hepatocytes using intraductal delivery and therefore, one of skill in the art would not reasonably regard intraductal delivery of recombinant vector as suitable means for efficient transfection of hepatocytes. Applicant further argues that, even if one of skill in the art would use the intraductal delivery route, one of skill in the art would use recombinant adenovirus and not naked DNA, because the art regards gene delivery by adenoviral vectors as more efficient than gene delivery by naked DNA. For these reasons, Applicant submits that Yang et al. teach away from the claimed invention. Regarding Hickman et al., Applicant submits that they teach away from administration routes other than direct injection into the liver, i.e., they teach away from the claimed invention. Applicant argues that Hickman et al. teach that only the hepatocytes near the site of injection were transfected and that the hepatocytes expressing the transgene were transfected by a physical mechanism related to the actual injection procedure (p. 1480, the top of column 2) and therefore, one of skill in the art would not look at the intraductal delivery of Yang et al.

as a suitable substitute for the injection of Hickman et al. Applicant argues that, because only hepatocytes near the site of injection were transfected with plasmid, one of skill in the art would not reasonably expect intraductal delivery of naked DNA to result in transfection of hepatocytes within the liver parenchyma, i.e., located outside of the hepatic duct. Therefore, one of skill in the art would not view the procedure of Hickman et al. amenable to the modification according to Yang et al. and therefore, the cited references do not provide a clear and particular motivation to combine. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments in his remarks and declaration are acknowledged, however, the rejection is maintained for the following reasons:

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Applicant's argument that Yang et al. teach away from the instant invention because they disclose biliary epithelial cells as the primary target for their transgene expression is not found persuasive. It is noted that Yang et al. teach gene therapy for cystic fibrosis (CF), a disease related to a defect in CF transmembrane conductance regulator (CFTR) expressed by the biliary epithelial cells and not by hepatocytes. The

goal of Yang et al. is to express CFTR only in the diseased cells because the art teaches that efficient gene therapy depends on specific delivery of transgenes to the target cells (in the instant case, biliary epithelial cells), without affecting the normal cells (in this case hepatocytes). To achieve this goal, Yang et al. performed experiments testing different dosed of adenoviral vectors that would result in specific gene delivery to the affected cells (i.e., biliary epithelial cells) for efficient therapy. However, this does not mean that they do not teach delivery to hepatocytes. On the contrary, Yang et al. teach that more than 80% hepatocytes can be transfected by using high doses of adenovirus (p. 4603, column 1, second paragraph) and that lowering the dose by 20-fold results in less than 1% transfected hepatocyte. Therefore, they clearly teach that hepatocytes can be transfected via intraductal delivery of adenoviral constructs and, depending of the dose used, the transfection could be very efficient (i.e., 80% when high adenoviral doses are used). Moreover, the art teaches that high transfection efficiencies are not necessary when genes encoding secreted proteins are used for therapy. For example, Losordo et al. teach that high transfection efficiencies are not required when dealing with secreted proteins, and that low transfection efficiencies result in a therapeutic effect in this case. Specifically, Losordo et al. teach that physiological levels of human growth hormone (hGH) can be achieved even when only rare cells were transfected by a plasmid encoding hGH (Abstract, p. 789, column 1, first full paragraph, p. 790, column 1 and Fig. 3). Therefore, by reading Yang et al. and Losordo et al., one of skill in the art would have known that even low transfection efficiencies could result in therapeutic levels of secreted proteins and would have known

to manipulate the dose of administered adenoviral constructs such that transduction of a desired number of hepatocytes is achieved. Therefore, Applicant's argument that, since Yang et al. teach inefficient transfection of hepatocytes via the intraductal route, one of skill in the art would not use this route is not found persuasive. With respect to Hickman et al., it is noted that they only suggest, and not clearly teach, that a physical mechanism is involved. One of skill in the art would readily recognize that the two means of delivery (direct injection and intraductal administration) operate via different mechanisms and would not extrapolate the results of Hickman et al. to intraductal delivery. Therefore, one of skill in the art would not consider that Hickman et al. teach away from the intraductal delivery. The argument that one of skill in the art would not reasonably expect intraductal delivery of naked DNA to result in transfection of hepatocyte is just an argument not supported by any evidence. Therefore, considering the cited references in their entirety, one of skill in the art would have known that: (i) the intraductal route could be used to deliver genes encoding for secreted proteins to the hepatic cells for delivery into the bloodstream and would have been motivated to use intraductal delivery of naked DNA in place of Hickman's approach of direct injection into the liver because Yang et al. clearly teach the advantage of intraductal delivery for gene therapy (p. 4603, column 2, Conclusions), (ii) manipulating the dose of administered DNA constructs would result in the desired number of transformed hepatocytes, and (iii) even low transfection efficiencies would result in physiological levels of secreted proteins (see also Hickman et al., who also teach that low transfection efficiencies result in delivery to the bloodstream). Applicant's argument that one of skill in the art would

not have been motivated to replace the adenovirus of Yang et al. with a naked DNA is not found persuasive because Hickman et al. clearly teach the disadvantage of using adenoviral vectors, even if naked DNA is not that efficient as an adenoviral vector (p. 1477 column 1 bridging p. 1478). Moreover, it is noted that the instant claims do not limit the amount of the DNA construct to be introduced intraductally, therefore one of skill in the art would have been able to introduce enough DNA construct to achieve hepatocyte transfection efficiency. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

It is noted that Hickman et al., taken with Yang et al. and Losordo et al. teach the same delivery method as the one claimed by the instant application and therefore the method must be as efficient as the claimed method in delivering proteins to the bloodstream.

9. Claims 31-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hickman et al. taken with Yang et al. and Losordo et al., in further view of Heartlein et al. (Proc Natl Acad Sci, 1994, 91: 10967-10971).

Applicant argues that Heartlein et al. do not discuss intraductal delivery of DNA into a secretory gland and therefore, they do not cure the deficiencies of Hickman et al. and Yang et al. Applicant submits that the Examiner did not establish a *prima facie* case of obviousness with respect to the teachings of Hickman et al. taken with Yang et al. for the same reasons presented above.

Applicant's arguments are acknowledged, however the rejection is maintained for the reasons set forth above. It is noted that Heartlein et al. reference was cited because it does teach that gene therapy can be used to treat HGH deficiencies. As stated in the prior Office Action, although Hickman et al., taken with Yang et al. do not teach HGH, one of skill in the art would have been motivated to use the method of Hickman et al., Yang et al., and Losordo et al. to deliver HGH to the bloodstream of a subject because Heartlein et al. do teach that growth hormone deficiencies can be treated by steady-state delivery of HGH via gene therapy. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

10. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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